REMARKS

The claim listing shown above reflects changes to the claims relative to the claim listing of the Amendment and Response After Final dated June 27, 2007 (which cancelled claims 1-3 and 5-10). In the amendments herein, claim 4 has been amended. Support for this amendment can be found throughout the specification as filed, e.g., at the paragraph bridging pages 28-29. Now pending in the application is claim 4. No new matter has been added.

The amendment and/or cancellation of claims is without prejudice or disclaimer of the subject matter thereof and was done solely to expedite prosecution of the present application. Applicants reserve the right to pursue the original subject matter of this application in a later filed application claiming benefit of the instant application, including without prejudice to any determination of equivalents of the claimed subject matter.

In view of the cancellation of claims 1-3 and 5-10, any rejections of these claims are moot and are not discussed further herein.

Rejection under 35 U.S.C. §112, first paragraph (enablement)

Claim 4 stands rejected under 35 U.S.C. §112, first paragraph, as allegedly failing to comply with the enablement requirement. This rejection is traversed. Applicants offer the following remarks.

Claim 4 is directed to method of evaluating onset or onset possibility of rheumatoid arthritis in a human subject, the method comprising the step of: detecting the presence or absence of a gene coding a protein comprising the amino acid sequence shown in SEQ. ID NO.:1 *homozygously* in the subject; and evaluating the onset or onset possibility of rheumatoid arthritis in the subject.

In Figure 4 of the subject application, the indicator "nt805(del3) homo" refers to the number of people having the normal gene homozygously, and the indicator "nt805(del3) hetero" refers to the number of people having the mutant gene heterozygously. In Figure 4, the indicator "nt805 homo" refers to the number of people having the mutant gene homozygously. In Figure 4, the label “Familial RA” refers to RA

patients from RA families (69 subjects in Table 4), and the label "Sporadic RA" refers to RA patients from sporadic families (225 subjects). The label "Familial not RA" refers to healthy subjects from RA families (28 subjects), and the label "Sporadic not RA" refers to healthy subjects from sporadic families (383 subjects). Thus, the total number of RA patients is 294 (the sum of "Familial RA" and "Sporadic RA"), and the total number of healthy subjects (the total of "Familial not RA" and "Sporadic not RA") is 411.

As discussed previously and as shown in Figure 4 of the application, both in RA families and Sporadic families, only the RA patients have "nt805 homo" (homozygous 3-base-insertion mutation). The Examiner appeared to agree that "it appears that an association exists for humans homozygous for the presence of 'GGT' at position 805-807" (Office Action at page 5). However, in the Advisory Action, the Examiner stated that the association between homozygous occurrence of the mutation and the presence of RA could be "an anomaly." Applicants disagree and provide the following data and discussion.

As described in the accompanying "Declaration Under 37 CFR 1.132" (the "Declaration"), in one experiment, PCR was performed as described to obtain a partial sequence of Angiopoietin-1 from whole RNA of whole blood of RA patients and healthy subjects. In this experiment, whole RNA was extracted from 300 µl of whole blood of each RA patient and healthy subject with the use of an RNA extraction kit provided by GENTRA system Inc. Using PCR methods, the presence or absence of insertion/deletion of the three bases No. 805 to No. 807 in the Angiopoietin-1 gene was determined.

The results of the experiment are shown in the Table in the Declaration, and indicate that the occurrence of the homozygous insertion mutation ("3bp insertion Homo") is associated with the occurrence of RA in the subjects studied (there is a "significant trend"). Applicants note that there were 33 RA subjects who had the "3bp insertion Homo" genotype.

In view of the data presented in the subject specification, and in the Declaration, Applicants contend that one of ordinary skill in the art would be able to evaluate the onset or onset possibility of rheumatoid arthritis in a human subject by detecting the

homozygous presence or absence of a gene coding a protein comprising the amino acid sequence shown in SEQ. ID NO.:1 (as described in the present application) in the subject, because the presence of the homozygous insertion mutation (the 3-base insertion at positions 805 to 807 in the nucleic acid sequence coding for Angiopoietin-1) is associated with rheumatoid arthritis, as described in the present application and in the experiment described herein.

Applicants respectfully contend that the specification provides enablement for the full scope of the pending claim, and, furthermore, that the claim meets all the requirements of, *inter alia*, 35 USC §112. Reconsideration and withdrawal of the rejection is requested.

CONCLUSION

For at least the above reasons, Applicants contend that the application is in condition for allowance. Early and favorable consideration of the application is earnestly solicited.

Applicants request any extension of time necessary for this response to be considered timely filed. The Director is hereby authorized to charge any deficiency in the fees filed, asserted to be filed or which should have been filed herewith (or with any paper hereafter filed in this application by this firm) to our Deposit Account No. 04-1105, under Reference No. 61646 (70904), Customer No. 21874.

Dated: September 11, 2007

Respectfully submitted,

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